**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY**
**DEPARTMENT OF PESTICIDE REGULATION**
**MEDICAL TOXICOLOGY BRANCH**

# SUMMARY OF TOXICOLOGY DATA

Propamocarb Hydrochloride

**Chemical Code #** 4022, **Tolerance #** 52084 and 50308
**SB 950 #** 302

**Original:** 12 September 2002
**Revised:** 6 March 2003

## I. DATA GAP STATUS

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|---|---|
| Chronic toxicity, rat: | No data gap, no adverse effect |
| Chronic toxicity, dog: | No data gap, possible adverse effect (tapetum lucidum of eye) |
| Oncogenicity, rat: | No data gap, no adverse effect |
| Oncogenicity, mouse: | No data gap, no adverse effect |
| Reproduction, rat: | No data gap, no adverse effect |
| Teratology, rat: | No data gap, possible adverse effect |
| Teratology, rabbit: | No data gap, no adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome effects: | No data gap, no adverse effect |
| DNA damage: | No data gap, no adverse effect |
| Neurotoxicity: | No data gap, no adverse effect |

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Toxicology one-liners are attached.

All record numbers through 202245 were examined.
** indicates an acceptable study.
**Bold face** indicates a possible adverse effect.
File name: T192184A
Prepared by T. Moore

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

** 054, 055 185194, 185195, "Propamocarb Hydrochloride Liquid Concentrate, Code: AE B066752 00 TK72 A101, Rat Combined Chronic Toxicity and Oncogenicity (Dietary)", (M. McFarlane and N. Buss, AgroEvo UK Limited, Toxicology, Essex, England, Report # TOX98/186-29, 17 December 1998). 70 Sprague Dawley CRL:CD (SD) BR rats per sex per group received Propamocarb Hydrochloride Liquid Concentrate (70.8%) in the diet at 0 (basal diet), 350, 2800, and 22400 ppm for 104 weeks. Mg/kg/day equivalents were 14.6 and 19.6, 118 and 158, and 958 and 1223 mg/kg/day for males and females respectively at 350, 2800, and 22400 ppm. An interim necropsy was performed on 20 per sex per group at 52 weeks. Statistically significant bodyweight reductions, 14%-23% for males and 14%-36% for females relative to controls, were noted at 22400 ppm. Food consumption was decreased for males (18% to 22%) and females (25% to 33%) at 22400 ppm. Water consumption was also reduced at weeks 9, 16, 32, and 48. Treatment related non-neoplastic changes were limited to the presence of vacuolation of the choroid plexus ependymal cells in both sexes at 22400 ppm (See supplemental overview, record 185195). Chronic NOEL = 2800 ppm (118 and 158 mg/kg/day equivalents for males and females respectively). **No oncogenicity/carcinogenicity noted. No adverse effects indicated**. Study previously unacceptable, possibly upgradeable with brain pathology protocol clarification. (Green and Gee, 8/5/02); letter of 10/16/02 from Dr. P.M. Millar confirmed that the areas of the brain specified in the guidelines (medulla/pons, cerebellar cortex, and cerebral cortex) were examined histologically; **Study acceptable.** (Moore, 3/5/03)

### CHRONIC TOXICITY, RAT

50308-018-019 & 013 058229-30 & 061589 "Previcur N (SN 66 752) Toxicity and Potential Tumorigenicity in Dietary Administration to Rats for 104 Weeks," (Brian Hunter, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # SHG/165-G/801056, 8/30/83). Previcur N (formulation with 76.1% technical propamocarb) was administered in diet to CD rats (50/sex/group) at 0, 40, 200 and 1000 ppm for 104 weeks. **No adverse effect indicated.** NOEL > 1000 ppm (no effects were observed in either sex at any dose level). **Not acceptable** (no MTD was reached and there was no justification for dose selection; high mortality in female control and 1000 ppm group). **Possibly upgradeable** (dose justification or a pilot study must be provided). An analysis of Previcur N (formulation) used in this study was provided in record 061589. M. Silva, 8/11/88.

### CHRONIC TOXICITY, DOG

**** 50308-014 & 013 058225 & 058223 and 52084-048 185188,** "24-Month Oral (Feeding) Toxicity Study With Previcur N in Beagle Dogs," (Dr. R. Bathe, Research & Consulting Company AG, Project # 003688, 6/6/85). Previcur N (formulated material; propamocarb purity = 68 to 68.7%) was administered in diet to Beagle dogs (6/sex/group) at 0 (vehicle = water), 1000, 3000 and 10,000 ppm for 24 months. NOEL = 3000 ppm (males showed a significant decrease in mean corpuscular hemoglobin after 18 months and after 21 months showed a significant increase in platelets; thrombin time was significantly increased in males after 2 months; aspartate aminotransferase was significantly increased in males and calcium was significantly decreased after 4 months; females showed a significant decrease in reticulocytes after 12 months and a significant increase in mean corpuscular hemoglobin count after 3 months). **Possible adverse effect** (irreversible degeneration of the tapetum lucidum was observed in all dogs at 10,000 ppm). **Acceptable.** An analysis of Previcur N (formulation) was presented in record 058223. M. Silva, 8/10/88. 52084-048 record 185188 contains duplicate and information to record 58225 and 58223. Part 3 of 52084-048, Record 185188, contains a discussion of the relevancy to humans

of the effect of propamocarb on the tapetum lucidum of dogs. The discussion was prepared by C. Marion Jackson, Schering Agrochemicals, November 1993. This particular eye structure is found in carnivorous vertebrates. Acting as a reflector in low light. Furthermore, no other ocular changes were noted, including in the retina and choroid using electron microscopy. (Green and Gee, 8/2/02).

## ONCOGENICITY, RAT

See Combined, rat.

## ONCOGENICITY, MOUSE

50308-015-017 & 013 058226-8 & 061589, "Previcur N (SN 66 752) Potential Tumorigenicity to Mice in Dietary Administration for 104 Weeks," (B. Hunter, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # SHG 164/80965/2, 8/30/83). Previcur N (formulated material containing 76.1% technical propamocarb) was administered in diet to CD-1 mice (60/sex/group) at 0, 20, 100 and 500 ppm (calculated as % technical propamocarb) for 104 weeks. **No adverse effect.** NOEL > 500 ppm (no effects were observed at any dose level in either sex). **Not acceptable** (an MTD was not reached in this study). **Possibly upgradeable** (DPR must be provided with a pilot study or justification for dose selection). An analysis of Previcur N (formulation) was provided in record 061589. M. Silva, 8/10/88.

**52084-053 185193, "Propamocarb HCL Liquid Concentrate, Code: AE B066752 00 TK72 A101, Mouse Dietary Oncogenicity (18 Months) Study", (Dr. R. Hammerl, Hoechst Marion Roussel Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Department of Toxicology/Pathology, Frankfurt am Main, Germany, Report # 98.0776,12 November 1998). 50 CD1 mice per sex per group received propamocarb hydrochloride liquid concentrate (71.2%) in the diet at 0, 0 (basal diet), 105, 840, and 6720 ppm for 18 months. Overall mg/kg/day equivalents calculated from food consumption and bodyweight were 15 and 17; 118 and 134; and 969 & 1240 mg/kg/day for males and females respectively at 105, 840, and 6720 ppm. Food consumption was increased for females at 6720 ppm. The increase was attributed to food spillage. Statistically significant reductions in bodyweight gain were noted for females at 840 and 6720 ppm from week 36 to termination. Bodyweight gain was decreased 12% and 15% for females at 840 and 6720 ppm respectively relative to controls through day 554. Chronic NOEL = 105 ppm (15 and 17 mg/kg/day equivalents for males and females respectively). No oncogenicity/carcinogenicity, no adverse effects. **Acceptable**. (Green, Gee, 8/5/02).

## REPRODUCTION, RAT

50308-010 043450, "Effect of Previcur N on Reproductive Function of Multiple Generations in the Rat", (P.A. Allen, Huntingdon Research Centre, Munster, Germany, Report # 126, 4/25/83). Propamocarb (Previcur N), batch #271001, B CP 604, approximately 70%; fed in the diet at 0, 40, 200 or 1000 ppm, to 25/sex/group, for 100 days to P generation before mating for F1A litters; NOEL $\geq$ 1000 ppm; **Unacceptable** (no evidence MTD was reached, analysis of diet presented but not identified by date or week, parental animals not necropsied, clinical obs not included.) No adverse reproductive effect and marginal decrease in food consumption. (J. Parker, 11/86).

50308-003 031162, One sentence summary of record 043450.

**52084-051, 052 185191, 185192 "Rat Dietary Two-Generation Reproductive Toxicity Study, Propamocarb Hydrochloride Liquid Concentrate 780 g/l", (Mark D. Nemec, WIL Research Laboratories, Inc, Ashland, OH., Report # WIL-303002, 18 December 1998). 30 Sprague-Dawley Crl:CD®(SD)BR rats per sex per group received propamocarb hydrochloride liquid concentrate in the diet at 0 (basal diet), 200, 1250, and 8000 ppm through 2 generations (1litter per generation). Treatment began 70 days prior to F0 mating. F1 generation parents were offered treated diet beginning on post partum day 22. F0 maternal bodyweight was reduced (statistically significant) at 8000 ppm during gestation and lactation. In the F1 generation, male and female mean

bodyweights were significantly lower than controls throughout the generation with statistical significance in females. Statistically significant decreases in food consumption were noted for F0 and F1 females at 8000 ppm throughout the study. Parental NOEL = 1250 ppm (81 mg/kg/day for males, 127 mg/kg/day for females). Reproductive NOEL = 8000 ppm (515 mg/kg/day for F0 and F1 males, 800 mg/kg/day for F0 and F1 females). Growth (weight gain) was decreased for F1 and F2 pups at 8000 ppm. Offspring NOEL = 1250 ppm. No adverse reproductive effects. **Acceptable**. (Green and Gee, 8/5/02).

52084-052 185192, "Rat Dietary Reproduction Range-Finding Study, Propamocarb Hydrochloride Liquid Concentrate 780 g/l", (Mark D. Nemec, WIL Research Laboratories, Inc., Report # WIL-303001, 18 December 1998). 10 Sprague-Dawley Crl:CD®(SD)BR rats per sex per group received propamocarb hydrochloride (71.1% purity) in the diet at 0 (basal diet), 5000, and 10000 ppm through 1 generation (1 litter). Treatment began 42 days prior to mating. After 2 weeks of treatment, the high dose level was increased to 15000 ppm since only minimal toxicity was seen at 10000 ppm. F0 male bodyweight and food consumption (statistically significant) was reduced at 10000/15000 ppm prior to mating. Statistically significant bodyweight and food consumption reductions were noted for F0 females pre-mating and during gestation and lactation at the high dose level, and at 5000 ppm during pre-mating. Mean live litter size, the number of implantation sites, pup weight, and pup growth were reduced at 10000/15000 ppm. Absolute and relative ovarian weights were decreased for F0 females at the high dose level. (H. Green, 5/16/02) (no worksheet).

## TERATOLOGY, RAT

****50308- 013, 009 061590, 043438 and 52084-049 185189,** "Previcur N (CP 604) Embryotoxicity Including Teratogenicity Study in Rats After Daily Intragastric Administration From Day 6 to Day 19 of gestation - TX 80.348; Report PF 62/81," (Schering AG, 11/2/81). Previcur N (formulation = 68% technical propamocarb; Code # ZK 66.752; batch #3005100 - CP 604) was administered by gavage to mated Wistar rats (25/group) at 0 (vehicle = water), 0.1, 0.3, 1.0 and 3.0 ml/kg from day 6-19 of gestation (day 0 = day vaginal plug or vaginal sperm detected). Maternal NOEL = 1.0 ml/kg (mortality, increased incidence of clinical signs and decreased weight gain in dams at 3.0 ml/kg). **Possible adverse effect.** Developmental NOEL = 0.3 ml/kg (increased % of fetuses with minor skeletal changes). Initially reviewed as unacceptable (J. Parker, 10/20/86), the status was changed to **acceptable** upon receipt of the requested analysis of dosing solutions (record 061590). M. Silva, 8/16/88. Record 185189 is duplicate information to record 61590 and 43438. (H. Green, 7/24/02).

## TERATOLOGY, RABBIT

50308-010 043448 "Previcur N Teratology Study Effect of Administration During Organogenesis on Foetuses of the Rabbit", (Huntingdon Research Centre, Munster Germany, Report # 143, 2/16/81) Previcur N, Code # SN66 752, batch #271001B CP 604, approximately 70% purity; tested at 0, 0.2, 0.4 or 0.8 ml/kg, by oral gavage, days 6-18 of gestation to 15-20 NZW rabbits/group; maternal NOEL = 0.2 ml/kg (body weight loss, abortion and death); developmental NOEL = 0.2 ml/kg (resorptions and decreased fetal weight). **Unacceptable**, not upgradeable (J. Parker,10/28/86).

50308-010, 013 043449, 061587-8 and 52084-050 185190 "Previcur N (CP 604) - Embryotoxicity Including Teratogenicity Study in Rabbits After Daily Intragastrical Administration From Day 6 to Day 18 of Gestation," (Schering Ag, Report # TX 80 122,1/9/81). Previcur N (formulation in aqueous solution; technical = 95.1%; code#: ZK 66.752; batch #271001 CP 604, 69.4% technical in formulation) was administered by gavage to mated New Zealand White rabbits (18-20/group) at 0 vehicle = water, 0.02, 0.06, 0.2, 0.4 or 0.8 ml/kg during days 6-18 of gestation (day 0 = confirmed vaginal smear). Maternal NOEL = 0.2 ml/kg (decreased body weight gain at 0.4 and 0.8 ml/kg). Developmental NOEL = 0.2 ml/kg (significantly decreased post-implantation loss). **Unacceptable** (not all fetuses examined viscerally and skeletally as required by current FIFRA

guidelines). **Not upgradeable.** J. Parker, 10/28/86. Subsequent information was submitted by Nor-Am Chemical Company: Record 061587 contained an analysis of dosing solutions and 061588 contained individual clinical data. This information was acceptable, however the study is still **not acceptable and not upgradeable** since all fetuses were not examined. M. Silva, 8/16/88. Record 185190 contains duplicate information to record 43449, 61587, and 61588. (H. Green, 7/24/02).

50308-003 31163 One-sentence summary of record 043449 (E.P.A. Acc. No. 245108) J.Gee 7/25/85

50308-008 22103 One-sentence summary of record 043449

**SUMMARY:** While neither of these studies complies fully with FIFRA guidelines, due to the number of dose levels evaluated in both studies, there are sufficient data available to adequately assess the potential toxicity of Previcur N. The registrant has supplied the additional data requested and it is acceptable, therefore these studies together fill the data gap for rabbit teratology.

## GENE MUTATION

50308-003/008 031159 One sentence summary of Ames test EPA ACC. # 237432. Maximum concentration of 2.5 ul, ± S9. Full study not on file with DPR. J.Gee, 7/25/85.

50308-009 043439 "Mutagenicity Testing of SN66.752", (R. Hastwell, Inveresk Research International, Report # 832, 8/77). Propamocarb, SN 66.752 (ZK.66.752) - CP 604, batch no. 270201 B00000, 70% purity; tested at 0, 3.5, 17.5, 87.5, 350 or 1750 ug/plate, in triplicate, 1 trial, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 ± S9 from rat liver; no evidence of cytotoxicity or mutation; **Unacceptable**, not upgradeable. No individual plate counts, no dose justification, and no repeat trial. J. Gee, 11/18/86.

50308-009 043443 "Previcur N Mutagenicity Evaluation in Yeast", (D.R. Jagannath, Litton Bionetics, 5/27/80) Previcur N, Batch no. 271001B00000, no purity stated, tested at 1000, 2500, 5000 or 10,000 ug/plate in triplicate, 1 trial, with *Saccharomyces cerevisiae* strains S138 and S211c, ± S9 from rat liver; no toxicity or mutation; **Unacceptable,** not upgradeable. No purity stated or repeat trial. J. Gee, 11/19/86.

50308-009 043445, 52084-061 185201, and 50308-013 058224, "T67 Propamocarb HCL: Mutagenicity Evaluation of Previcur N in the Gene Conversion and Reverse Mutation Assays with *Saccharomyces Cerevisiae* Strains D4, S138 and S211a", (A.J.W. Hoorn, Litton Bionetics, The Netherlands, Report # E-9409, 24 October 1985). *Saccharomyces cerevisiae* strains S138 and S211a were exposed overnight in liquid culture in quadruplicate to Previcur N (68.9% propamocarb technical) at 0 (water), 1.0, 5.0, 10.0, 12.5, 15.0, 20.0, and 25 ul/ml in the presence of S9 activation. No increase in the number of revertants or reversion frequencies. **Unacceptable** (no purity and no individual plate counts), (J. Gee, 11/18/86). Records 185201 and 058224 provide test article purity and individual plate counts. Study status remains **unacceptable** and **not upgradeable** since no cultures were tested in the absence of activation. (Green and Gee, 8/7/02).

50308-013 061585 Appendix 3 contains an analysis of Previcur N (formulation) batch no. 271001 S 00000 used in records 043442-4. M. Silva, 8/15/88.

50308-013 061586 This submission contains a duplicate copy of the protocol and methods for "Reverse Mutation Induction in Saccharomyces Cerevisiae Strains S138 and S211" originally found in record 043443.

**52084-056 185196, "Technical Propamocarb Hydrochloride: Microbial Metabolic Activation Test to Assess Mutagenic Potential", (Eryl Jones and Lesley A. Fenner, Huntingdon Research Centre, Cambridgeshire, England, 11 August 1987). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* strain WP2 uvrA were exposed to Technical propamocarb hydrochloride, in the presence and absence of S9, at 0 (solvent, 0.1 M HCL), 0 (bacteria plus buffer only, no solvent), 15, 50, 150, 500, 1500, and 5000 :g/plate for 72 hours in two separate trials. No increase in the mutation reversion frequency. **Acceptable**. (Green and Gee, 8/7/02).

**52084-057 185197, "In Vitro Mammalian Cell Mutation Test with Mouse Lymphoma Cells", (M. Gillian Clare, Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England, Report # AES 004/003525, 27 April 2001). L5178Y mouse lymphoma cells (subline 3.7.2c) were exposed in duplicate cultures (solvent controls in quadruplicate) to Propamocarb Hydrochloride Liquid Concentrate 780 g/l (technical, 71.1%) in the presence and absence of S9 activation in two trials. In the first trial, 3 hour exposures at 0 (purified water), 125, 250, 500, 750, 1000, 1250, 1875, and 2500 :g/ml were conducted in the presence and absence of S9. In the second trial, 3 hour treatment was conducted with S9 activation at 0, 500, 1000, 1500, 2000, 2500, 300, 3500, and 4000 :g/ml. Non-activated exposure was at 0, 100, 200, 400, 600, 800, 1000, 1500, and 2000 :g/ml for 24 hours with a repeat trial. The microtitre method was used to determine cytotoxicity and mutant frequency. Mutation frequencies at the thymidine kinase locus did not increase with statistical significance under test conditions using trifluorothymidine to select. **Acceptable.** (Green and Gee, 8/7/02).

## CHROMOSOME EFFECTS

**50308-009 & 013 043440, 061583 & 061585 and 52084-060 185200, "Micronucleus Test on CP 604 (SN 66752, Previcur N)," (David J.N. Hossack, *et al*., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # SHG 182/79183, 1/22/80). Previcur N (formulation containing 76.1% propamocarb) was administered by gavage to CFLP mice (5/sex/group) in 2 equal dosages, separated by an interval of 24 hours at 0 (vehicle = 1% methylcellulose), 1250, 2500 and 5000 mg/kg. The mice were killed 6 hours after the 2nd dose. In a second test, 5 mice/sex/group were tested at 0 and 2500 mg/kg and the mice were killed at 12, 24, 36 and 48 hours after the 2nd dose. **No adverse effect indicated.** No significant chromosome damage was observed in either test. Positive controls functioned as expected. This study was previously reviewed as unacceptable by J. Gee, 11/18/86 (No purity statement, single sampling time at 6 hours) but was upgraded to **acceptable** upon receipt and review of the entire study (record 061583) at DPR**.** An analysis of Previcur N (formulated) was in record 061585. M. Silva, 8/12/88. Record 185200 is duplicate information to record 43440, 61583, and 61585. (H. Green, 7/24/02).

50308-003 031160 One sentence summary of record 43440. J. Gee 7/25/85

50308-003 031161 One sentence summary of record 43441. J. Gee, 7/25/85.

50308-009 043441, "Dominant Lethal Study of Previcur N", (Ted A. Jorgenson, SRI International, Menlo Park, CA., Report # LSC-8516, 11/79). Previcur N, Code #SN 66 752, batch #27 1001 B, Recipe No. CP 604), 69.2% purity, tested at 0, 500, 1000, 2000, 4000 or 8000 ppm in drinking water for 8 weeks to 20 ICR/SIM mice/group; dose-related decreases in water consumption and body weights, and no dominant lethal effects observed; **Unacceptable,** upgradeable. No analyses of drinking solutions. J. Gee, 11/18/86.

52084-058 185198, "Technical Propamocarb Hydrochloride (Previcur N): Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*", (J. A. Allen, *et al*., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # SMS 54/87808, TOX 87/186-

13 15 July 1987). Human lymphocytes (source not given) were incubated for 48 hours with phytohemagglutinin stimulation, then exposed in duplicate cultures (solvent and medium controls in quadruplicate) to Technical propamocarb hydrochloride (69%) at 0 (solvent), 0 (culture medium), 110, 550, 825, and 1100 :g/ml in the absence of S9 and at 0 (solvent), 0 (culture medium), 470, 2350, and 4700 :g/ml with S9. A 2 hour exposure period was used with activation. Non-activated treatment duration was (apparently) 24 hours. Positive controls were functional. No increase in clastogenic activity. **Unacceptable**, upgradeable (justification for no confirmatory trial -S9). (Green and Gee, 8/7//02).

**52084-059 185199, "Micronucleus Test on CP 604 (SN66752, Previcur N)", (David J. N. Hossack, *et al*., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # SHG 191/79737, 26 February 1980). 20 CD-1 mice per sex received Previcur N technical (76.1% propamocarb hydrochloride) by gavage at 0 (1% methylcellulose) and 1250 ppm twice with a 24 hour interval. Bone marrow from 5 per sex was sampled at 12, 24, 36, and 48 hours after the second dose with 2000 erythrocytes scored per animal. Positive controls were functional. No increase in micronuclei. **Acceptable.** (Green and Gee, 8/8/02).

## DNA DAMAGE

50308-009 043442 & 043444, "Mitotic Gene Conversion in Saccharomyces Cerevisiae Strain D4", (Litton Bionetics, 5/27/80). Previcur N, Batch no. 271001B00000, no purity stated, tested at 1000, 2500, 5000 or 10,000 ug/plate in triplicate, 1 trial, strains $D_4$and $D_5$, ± S9 from rat liver; no toxicity or mutation; **Unacceptable,** not upgradeable. No purity stated or repeat trial. J. Gee, 11/19/86.

50308-009, 013 043446, 058224 and 52084-061 185201, "T67 Propamocarb HCL: Mutagenicity Evaluation of Previcur N in the Gene Conversion and Reverse Mutation Assays with *Saccharomyces Cerevisiae* Strains D4, S138 and S211a", (A.J.W. Hoorn, Litton Bionetics, The Netherlands, Report # E-9409, 24 October 1985). *Saccharomyces cerevisiae* strain D4 was exposed overnight in liquid culture in quadruplicate to Previcur N (68.9% propamocarb technical) at 0 (water),10.0, 12.5, 15.0, 20.0, 25.0, 30.0, and 33.3 ul/ml in the presence of S9 activation. No gene conversion induction. **Unacceptable** (no purity and no individual plate counts), (J. Gee, 11/18/86). Updated (M. Silva, 8/17/88) with record 058224 that includes test article purity and individual plate counts. No change in status. **Unacceptable** and **not upgradeable** (no non-activated cultures). Record 185201 provides Certificate of test article analysis and individual plate counts. Study status remains **unacceptable** and **not upgradeable** (no non-activated assay). (Green and Gee, 8/7/02).

**SUMMARY:** While neither study fully complies with guidelines, taken together they fill the data gap (record# 043446 is a partial repeat of 043442, -44). The registrant has submitted the requested data and they are acceptable (records 058224 and 185201).

## NEUROTOXICITY

037, -038, -047, -108; 185177, 185178, 185187, 202243; "T87 Propamocarb: Rat Acute Oral Neurotoxicity Study" (Ponnock, K.S., Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ, Laboratory Project ID TOX/93/186-30, 11/1/93). 821. Previcur N SL (code/batch number CR 18131/01/911202, 711 g/l a.i.), prepared in distilled water, was administered as a single gavage dose to 10 CD® (Sprague Dawley derived) [CRL: CD® BR] rats per sex per dose at dose levels of 0 (vehicle only), 28.1 (a.i. concentration = 20), 281.0 (200), and 2813.0 (2000) mg/kg. The animals were observed for 22 days following dosing. No animals died. No effects on body weight were observed. No clinical signs were observed. Treatment-related soiled coat during FOB and decreased motor activity were observed on Day 1 (within 8 hours of treatment) in females at 2813.0 mg/kg. No treatment-related effects were observed during FOB and motor activity assessments conducted on Day 8 and on Day 15. Macroscopic and

microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 2813 mg/kg (a.i. = 2000 mg/kg) (based on no effects at the highest dose tested), NOEL (F) = 281 mg/kg (a.i. = 200 mg/kg) (based on soiled coat observed during FOB and decreased motor activity). **Acceptable.** (Corlett and Leung, 2/21/03, **upgraded from unacceptable,** (Corlett and Leung, 8/1/02) with the submission of required positive control data)

039; 185179; "T86 Propamocarb: Rat Acute Neurotoxicity Study Range-Finding Study" (Ponnock, K.S., Pharmaco LSR Inc., Toxicology Services, North America, East Millstone, NJ, Laboratory Project ID TOX/93/186-29, 10/29/83). Previcur N SL (code/batch number CR 18131/01/911202, 711 g/l a.i.), prepared in distilled water, was administered as a single gavage dose to 2 CD® (Sprague Dawley derived) [CRL: CD® BR] rats per sex per dose at dose levels of 0, 351.5 (a.i., 250), 703 (a.i., 500), 1406.5 (a.i., 1000), and 2813 (a.i., 2000) mg/kg. The animals were observed for 6 days following dosing. No animals died. No effects on body weight were observed. No clinical signs were observed. Assessments of behavior (including response to external stimuli), neuromuscular coordination, reflexes, and of major body functions such as respiration, excretion, and physical appearance that were evaluated at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, and 24 hours after dosing revealed no effects. **No adverse effects.** NOEL (M/F) = 2813 (a.i., 2000) mg/kg based on no effects at the highest dose tested. **Supplemental** (only 2 animals per sex per dose were used, animals were observed only for 6 days, no necropsies were performed, and no histopathology was performed). (Corlett, 8/1/02)

044, -045, -108, 185184, 185185, 202243; "Previcur N SL: Rat Subchronic (3-Month) Dietary Neurotoxicity Study" (Ponnock, K.S., Pharmaco LSR Inc., Toxicology Services North America, East Millstone, NJ, Sponsor's Study No. TOX/92006, 11/1/93). 827. Previcur N SL (code/batch number CR 18131/01/911202, 711 g/l a.i.) was admixed to the feed and fed to 10 CD® (Sprague Dawley derived) [CRL: CD® BR] rats per sex per dose at dose levels of 0 (diet only), 281 (a.i. concentration = 200), 2813 (2000), and 28129 (20000) ppm (0, 18.2, 189.3, 1857.7 mg/kg/day, respectively, for males, and 0, 20.0, 208.8, 2089.4 mg/kg/day, respectively, for females) for a period of at least 90 days. All animals survived to scheduled sacrifice. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight was observed in both sexes at 28129 ppm. No treatment-related effects were observed during FOB assessments. Motor activity assessments revealed no treatment-related effects. No statistically significant decreases in group mean plasma or erythrocyte cholinesterase values were observed at Week 4 or at study termination. No statistically significant decreases in group mean brain cholinesterase values were observed at study termination. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 189.3 mg/kg/day (2813 ppm (a.i. concentration = 2000 ppm)) and NOEL (F) = 208.8 mg/kg/day (2813 ppm (a.i. concentration = 2000 ppm)) based on a decrease in mean body weight. **Acceptable.** (Corlett and Leung, 2/21/03, **upgraded from unacceptable**, Corlett and Leung, 8/1/02, with the submission of required positive control data).

## METABOLISM

52084-062, 063 185202, 185203, "M19 Propamocarb: Previcur N CR 18131 Metabolism in the Rat", (C.M.M. Reynolds, AgrEvo UK limited, Essex, UK., Report # TOX/93/186-33 and TOX/91141, 7 July 1994) and "M19 Addendum 1, Propamocarb: Mass Spectrometric Investigation of Metabolites in Rat Urine", (D.R. Hawkins, *et al*., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # SMS 502/942265 and TOX/91141, 13 May 1994). Separate groups (5 per sex) of rats (strain not identified) received single oral gavage doses of [$^{14}$C] propamocarb hydrochloride (in distilled water) at 10 and 1000 mg/kg. Another group received a single oral dose of radiolabelled [$^{14}$C] propamocarb hydrochloride at 10 mg/kg preceded by 14 consecutive daily doses of unlabelled test article. In another phase, rats received a single intravenous dose of [$^{14}$C] propamocarb hydrochloride (in isotonic saline). The main route of elimination was in the urine. 70% to 91% of the radiolabelled dose was eliminated in the urine over 24 hours and 78% to 96% over 72 hours post-dosing. Excretion in the feces accounted for 2% to 5%. Nine peaks were found in the high performance liquid chromatography (HPLC)

analysis for metabolites. Five of the metabolites were identified. Metabolism involved aliphatic oxidation of the propyl chain, N-oxidation of the tertiary amine and N-dealkylation. Record 185203 is an addendum that contains analyses of the separation of 6 radioactive components of a urine sample from one rat by high performance liquid chromatography and the mass spectrometric analyses identifying 5 compounds: propamocarb hydrochloride; propamocarb-N-Oxide; 3-(3-dimethylaminopropyl)-4-hydroxy-4-methyl-oxazolidin-2-one; 2-hydroxypropamocarb; and mono-N-desmethylpropamocarb. **Unacceptable** and not upgradeable (incomplete protocol, no tissue distribution, no plasma kinetics, others). (Green and Gee, 8/8/02).

52084-0110; 202245; "Propamocarb HCl: Absorption, Distribution, and Elimination, Studies in the Rat following Single and Repeated Oral Dosing and Single Intravenous Dosing"; (C.M.M. Reynolds; Schering Agrochemicals Ltd., Safety Evaluation, Chesterford Park, Saffron Walden, Essex, CB10 1XL, UK; Study Nos. TOX/91137, 91138, 91139, 91140; 2/2/94); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with a single dose of (A) 10 or (B) 1000 mg/kg or (C) 15 doses of 10 mg/kg/day or a single intravenous dose of (D) 10 mg/kg of $^{14}$C]-Propamocarb HCl, (free base) batch nos. 1795-2, 1795-2A, radiochemical purity: >98%, specific activity: 156 uCi/mg, (used in (A) and (B)), (HCl) batch no. DR 93/6/AV-1, radiochemical purity: > 98%, specific activity: 225 uCi/mg, (used in (C) and (D)); non labeled propamocarb HCl (Previcur N), batch no. ZK 66752, a.i.: 708.0 g/l (used in (A) and (B)), batch no. 410818, a.i.: 718.0 g/l (used in (C)), batch no. 410818, a.i.: 717.0 g/l (used in (D)). Urine and fecal samples were collected at designated times up to 48 (A) or 72 (B, C, and D) hours post-dose. Urinary excretion was the major path of elimination with 78 to 95% of the administered dose recovered in the urine within 48 or 72 hours post dose. Seventy eight to 93% of the administered dose was excreted within 24 hours. The liver was the primary site of recovery in the tissues. There were no apparent differences between the sexes or the route of administration. Entry across the blood/brain barrier was not apparent. **Study acceptable.** (Moore, 3/5/03)

## SUBCHRONIC STUDIES

### (90-day feeding study)

040, 185180; "Rat Dietary 90-Day Toxicity Range Finding Study Propamocarb Hydrochloride Liquid Concentrate" (Hubbard, K., Centre International deToxicologie, Miserey, France, Study Identification TOX 94155, Report No. TOX/98/186-36, 12/17/98). 821. Propamocarb Hydrochloride Liquid Concentrate (Batch No. 06446179, 71.2% w/w a.i.) was admixed to the diet and administered to 10 Crl CD (SD) BR rats per sex per dose at dose levels of 0 (untreated diet), 7020 (a.i. concentration = 5000), 14040 (10000), and 28080 (20000) ppm (0, 447 (318), 908 (646), 1915 (1363) mg/kg/day, respectively, for males, and 0, 510 (363), 1005 (716), 2176 (1549) mg/kg/day, respectively, for females) for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight was observed in females at 14040 (10000) ppm and in both sexes at 28080 (20000) ppm. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 908 (a.i. concentration = 646) mg/kg/day (14040 ppm (a.i. concentration = 10000 ppm)) and NOEL (F) = 510 (363) mg/kg/day (7020 ppm (5000 ppm)) based on a decrease in mean body weight. **Acceptable**. (Corlett, 8/30/02)

041, 185181; "Mouse Dietary 90-Day Toxicity Range Finding Study Propamocarb Hydrochloride Liquid Concentrate" (Hubbard, K., Centre International deToxicologie, Miserey, France, Study Identification TOX 94156, Report No. TOX/98/186-37, 12/17/98). Propamocarb Hydrochloride Liquid Concentrate (Batch No. 06446179, 71.2% w/w a.i.) was admixed to the diet and administered to 10 Crl: CD-1 (1CR) BR mice per sex per dose at dose levels of 0 (untreated diet), 1404 (a.i. concentration = 1000), 2808 (2000), 5616 (4000), and 11232 (8000) ppm (0, 238 (169), 479 (341), 939 (669), 1895 (1349) mg/kg/day, respectively, for males, and 0, 295 (210), 657 (468), 1311 (933), 2742 (1952) mg/kg/day, respectively, for females) for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)=

1895 (a.i. concentration = 1349) mg/kg/day (11232 ppm (a.i. concentration = 8000 ppm)) and NOEL (F) = 2742 (1952) mg/kg/day (11232 ppm (8000 ppm) based on no effects at the highest dose tested. **Supplemental study** (since serum chemistry and hematology were not performed on the test animals). (Corlett, 9/4/02)

042; 185182; "T32 Propamocarb HCl: Subchronic (90 Day) Feeding Study with ZK 17.296 in Dog" (Reuzel, P.G.J. and Til, H.P., Central Institute for Nutrition & Food Research, Laboratory Project ID R5178, 1/77). ZK 17. 296/SN 39.744/CP 492.100 S (70% a.i.) was admixed to the diet and administered to 4 pure-bred beagle dogs per sex per dose at dose levels of 0, 50, 100, 500, or 1000 ppm /increased to 2000 ppm at week 7 for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F) = 40 mg/kg/day (1000 ppm) based on no effects at the highest dose tested. **Supplemental** (no dosing material analysis was presented, statistical analyses were not performed on the means of animals of each sex at each dose level but on the means of males and females combined at each dose level, and no ophthalmological examinations were performed on the animals). (Corlett, 9/6/02)

**(Dermal)**

043, 185183; "Previcur N (Propamocarb HCl)- Rat 21-Day Dermal Repeat Dose Study" (Healing, G., Safety Evaluation Department of Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron Walden, Essex, UK, Study No. TOX/91235, Report No. TOX/92/186-16, 7/15/92). 822. Previcur N (Propamocarb HCl) (Batch/code No. CR 18131/01/911202, a.i. content = 716.9 g/l) applied to the clipped dorsal skin of 5 Sprague Dawley CRL: CD (SD) BR rats per sex per dose at dose levels of 0, 100, 500, or 1000 mg/kg/day for 6 hours per day, 5 days per week over a 21 day period. No mortalities occurred. No treatment-related systemic clinical signs were observed. Treatment-related abrasions at the test site were observed in both sexes at 500 and 1000 mg/kg/day. Microscopic examination of the skin revealed treatment-related acute inflammatory infiltration, epidermal hyperplasia, ulceration, and eschar in both sexes at 500 and 1000 mg/kg/day. Macroscopic and microscopic examinations revealed no treatment-related internal organ abnormalities. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F, skin) = 100 mg/kg/day based on acute dermatitis and other skin effects. **Acceptable**. (Corlett, 9/11/02)